SEARCH REQUEST FORM

Scientific and Technical Information Center

MAY 16 2

Requester's Full Name: Rosalynn C. Jones Examiner #: 71991 Date: 16 MAY 03

Art Unit: 1614 Phone Number 305-4691 Serial Number: 10/082,864

Mail Box and Bldg/Room Location: 2007, CM1 Results Format Preferred (circle): PAPER DISK E-MAIL

2007, CM1

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: see attached sheet

Inventors (please provide full names): "

"

Earliest Priority Filing Date: 23 FEB 2001

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search claims 1-3 & 5

Point of Contact:
Barb O'Bryen
Technical Information Specialist
STIC CM1 6A05 308-4291

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: BOB	NA Sequence (#)		STN	274
Searcher Phone #:	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)		Questel/Orbit	
Date Searcher Picked Up:	Bibliographic	X	Dr.Link	
Date Completed: 5-22-03	Litigation		Lexis/Nexis	
Searcher Prep & Review Time: 20	Fulltext		Sequence Systems	
Clerical Prep Time:	Patent Family		WWW/Internet	
Online Time: 61	Other		Other (specify)	

PTO-1590 (8-01)

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We claim:

1. A method of inhibiting the growth of a tumor in a mammal, wherein the growth of the tumor depends on basic fibroblast ~~growth~~ factor-stimulated angiogenesis, said method comprising administering to the mammal a therapeutically effective amount of a bFGF-active PAF antagonist.

2. The method of claim 1, wherein the bFGF-active PAF antagonist comprises tetrahydro-4,7,8,10 methyl-1 (chloro-2 phenyl)-6 (methoxy-4 phenyl-carbomoyl)-9 pyrido [4',3'-4,5] thieno [3,2-*f*] triazolo-1,2,4[4,3-*a*]diazepine-1,4 ("BN-50730").

LAU 8080
Rocepafant

3. The method of claim 1, wherein the bFGF-active PAF antagonist comprises CV 3988.

4. The method of claim 1, additionally comprising the step of administering to the mammal an additional compound that inhibits tumor angiogenesis.

5. The method of claim 4, wherein the additional compound is chosen from a group comprising WEB 2086, INF-2α, TNP-470, endostatin, SU 5416, SU 6668, batimistat, angiostatin, and celecoxib.

6. The method of claim 1, wherein said administering of the bFGF-active PAF antagonist is performed by subcutaneous injection, intravenous injection, intraperitoneal injection, or transdermal absorption.

7. The method of claim 1, wherein the mammal is a human.

8. The method of claim 1, wherein the tumor is chosen from a group comprising carcinomas of the lung, breast, colon, stomach, pancreas, skin, uterus, cervix, vagina penis, mouth, larnyx, esophagus, liver, kidney or prostate; sarcomas of the muscle or connective tissue; osteosarcomas; neuroblastomas; glioblastomas; neuroblastomas; Hodgkin's disease lymphomas; non-Hodgkin's lymphomas; B-cell lymphomas; T-cell lymphomas; acute lymphocytic leukemias; chronic myloid leukemia; acute myloid leukemia; and non-malignant tumors.

9. The method of claim 8, wherein the tumor is a form of carcinoma of the lung.

10. The method of claim 8, wherein the tumor is a form of carcinoma of the prostate.

ABSTRACT OF THE DISCLOSURE

A novel use of platelet-activating factor antagonists that bind to intracellular PAF binding sites such as BN-50730 (tetrahedra-4,7,8,10 methyl-1 (chloro-1 phenyl)-6 (methoxy-4 phenyl-carbamoyl)-9 pyrido [4',3'-4,5] thieno [3,2-*f*] triazolo-1,2,4 [4,3-*a*] diazepine-1,4) has been discovered. These intracellular-binding platelet-activating factor antagonists were found to inhibit both *in vivo* and *in vitro* tumor growth and angiogenesis where the angiogenesis is stimulated by basic fibroblast growth factor.

The structure of BN-50730

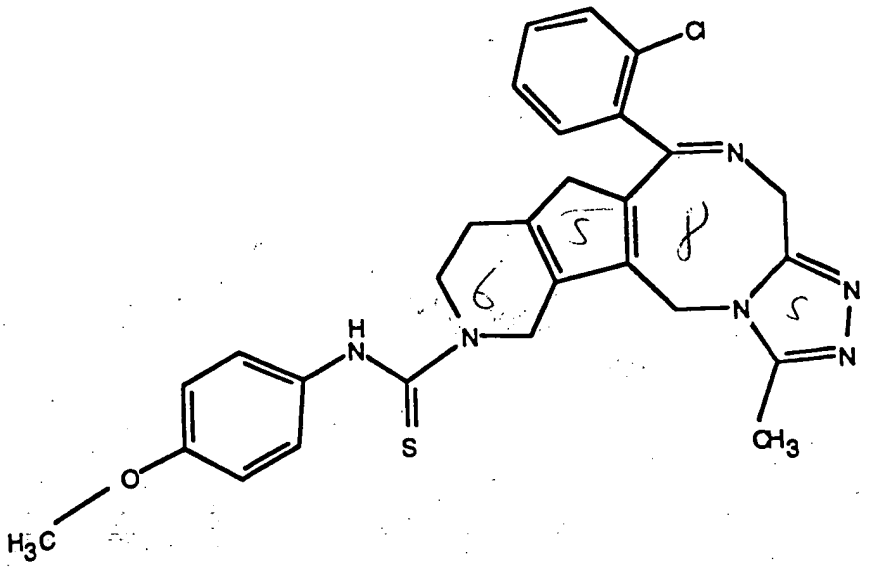

Fig. 1

514/211.09

218

219

PATENT NUMBER and ISSUE DATE

U.S. UTILITY Patent Application

APPL NUM	FILING DATE	CLASS	SUBCLASS	GAU	EXAMINER
10082821	02/25/2002	514	285	1614	Gr~~ou~~ Jones, D

**APPLICANTS: Hunt Jay; Bazan Haydee E.; Marcheselli Victor L.; Builla Gomez Julio; Bazan Nicholas;

**CONTINUING DATA VERIFIED:
THIS APPLN CLAIMS BENEFIT OF 60/271,286 02/23/2001

** FOREIGN APPLICATIONS VERIFIED:

PG-PUB	DO NOT PUBLISH ☐	RESCIND ☐	
Foreign priority claimed	☐ yes ☐ no		ATTORNEY DOCKET NO
35 USC 119 conditions met	☐ yes ☐ no		00M28. 1 Hunt
Verified and Acknowledged Examiners's intials			

TITLE : Platelet-activating factor antagonist inhibition of angiogenesis and tumor growth induced by basic fibroblast growth factor

U.S.DEPT. OF COMM./PAT.& TM-PTO-436L(Rev. 12-94)

NOTICE F ALLOWANCE MAILED	Assistant Examiner	CLAIMS ALLOWED	
		Total Claims	Print Claim for O.G
ISSUE FEE		DRAWING	
Am unt Due / Date Paid		Sheets Drwg. / Figs Drwg. / Print Fig.	

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=> fil reg; d ide l4; d ide l5
FILE 'REGISTRY' ENTERED AT 11:46:27 ON 22 MAY 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   20 MAY 2003  HIGHEST RN 518004-10-9
DICTIONARY FILE UPDATES:  20 MAY 2003  HIGHEST RN 518004-10-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf


L4   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   132579-32-9  REGISTRY
CN   4H-Pyrido[4',3':4,5]thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine-
     9(8H)-carbothioamide, 6-(2-chlorophenyl)-7,10-dihydro-N-(4-methoxyphenyl)-
     1-methyl- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   6-(o-Chlorophenyl)-7,10-dihydro-1-methylthio-4H-
     pyrido[4',3':4,5]thieno[3,2-f]-s-triazolo[4,3-a][1,4]diazepine-9(8H)-
     carboxy-p-anisidide
CN   BN 50730
CN   LAU-8080
CN   Rocepafant
FS   3D CONCORD
DR   132418-36-1
MF   C26 H23 Cl N6 O S2
SR   CA
LC   STN Files:   ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CANCERLIT,
       CAPLUS, CASREACT, DRUGNL, DRUGPAT, DRUGUPDATES, EMBASE, IPA, MEDLINE,
       PHAR, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   WHO
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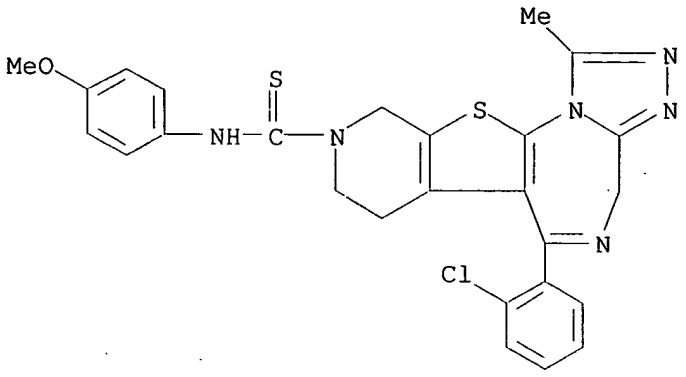
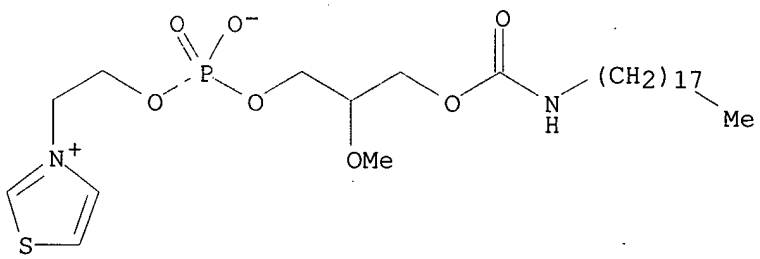


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

46 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
47 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **85703-73-7** REGISTRY
CN Thiazolium, 3-(4-hydroxy-7-methoxy-4-oxido-10-oxo-3,5,9-trioxa-11-aza-4-phosphanonacos-1-yl)-, inner salt (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Thiazolium, 3-(4-hydroxy-7-methoxy-10-oxo-3,5,9-trioxa-11-aza-4-phosphanonacos-1-yl)-, inner salt, P-oxide, (.+-.)-
OTHER NAMES:
CN CV 3988
DR 80350-07-8
MF C28 H53 N2 O7 P S
LC STN Files: ADISINSIGHT, AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CHEMCATS, CSCHEM, DDFU, DRUGU, EMBASE, IPA, MEDLINE, PHAR, PROMT, SYNTHLINE, TOXCENTER, USPATFULL, VETU
(*File contains numerically searchable property data)



99 REFERENCES IN FILE CA (1957 TO DATE)
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FILE COVERS 1907 - 22 May 2003  VOL 138 ISS 21
FILE LAST UPDATED: 21 May 2003  (20030521/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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L5            1 SEA FILE=REGISTRY ABB=ON  85703-73-7
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L12          90 SEA FILE=HCAPLUS ABB=ON  L4 OR (BN50730 OR BN 50730 OR LAU8080
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                 OR SUBSTANCE#)/OBI
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L20        7968 SEA FILE=HCAPLUS ABB=ON  BASIC FIBROBLAST GROWTH FACTOR
L21       20473 SEA FILE=HCAPLUS ABB=ON  ?ANGIOGEN? OR ?NEOVASCULAR?
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=> s l14 or l22 or l35

L106        10 L14 OR L22 OR L35

=> fil medl; d que l42; d que l44; d que l45; d que l50

FILE 'MEDLINE' ENTERED AT 12:42:36 ON 22 MAY 2003

 FILE LAST UPDATED: 21 MAY 2003 (20030521/UP).  FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

 This file contains CAS Registry Numbers for easy and accurate
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=> fil drugu; d que l60; d que l61; d que l71

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FILE LAST UPDATED: 22 MAY 2003       <20030522/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001.  <<<
>>>  (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION     <<<
>>>  SEE HELP COST                                       <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<



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L56         274 SEA FILE=DRUGU ABB=ON  L5 OR CV3988 OR CV 3988
L58      119695 SEA FILE=DRUGU ABB=ON  NEOPLASM+NT/CT
L60           4 SEA FILE=DRUGU ABB=ON  L58 AND (L55 OR L56)



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L58       119695 SEA FILE=DRUGU ABB=ON  NEOPLASM+NT/CT
L61            5 SEA FILE=DRUGU ABB=ON  L58 AND (L55 OR L56 OR L57) AND (L53 OR
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L69           24 SEA FILE=DRUGU ABB=ON  (L57 OR L63) AND L58
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=> s l60 or l61 or l71

L108           9 L60 OR L61 OR L71

=> fil embase; d que l81; d que l82; d que l85; d que l88

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 FILE COVERS 1974 TO 19 May 2003 (20030519/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

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 substance identification.


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L77      1121786 SEA FILE=EMBASE ABB=ON  NEOPLASM+NT/CT
L80       139295 SEA FILE=EMBASE ABB=ON  L77(L)DT/CT - DT = drug therapy
L81            1 SEA FILE=EMBASE ABB=ON  L80 AND (L73 OR L74)


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L82            9 SEA FILE=EMBASE ABB=ON  L77/MAJ AND (L73 OR L74)


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L87      229276 SEA FILE=EMBASE ABB=ON  DRUG COMBINATION/CT
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=> s l81 or l82 or l85 or l88

L109         13 L81 OR L82 OR L85 OR L88

=> fil wpids; d que l97;d que l102

FILE 'WPIDS' ENTERED AT 12:42:42 ON 22 MAY 2003
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FILE LAST UPDATED:          16 MAY 2003      <20030516/UP>
MOST RECENT DERWENT UPDATE:     200331        <200331/DW>
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L89           6 SEA FILE=WPIDS ABB=ON  (BN50730 OR BN 50730 OR LAU8080 OR LAU
                8080 OR ROCEPAFANT)
L90           1 SEA FILE=WPIDS ABB=ON  CV3988 OR CV 3988
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DT = drug therapy
AD = administration ~~& dosage~~
PK = pharmakokinetics
DO = dosage
PD = pharmacology

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L95       58334 SEA FILE=WPIDS ABB=ON  ?CANCER? OR ?NEOPLAS? OR ?LEUKEMI? OR
                ?LEUKAEMI? OR ?CARCINOM? OR ?LYMPHOMA? OR ?SARCOMA? OR
                ?GLIOMA?
L96       42937 SEA FILE=WPIDS ABB=ON  ?TUMOR? OR ?TUMOUR?
L97           1 SEA FILE=WPIDS ABB=ON  (L89 OR L90) AND (L95 OR L96)



L91         380 SEA FILE=WPIDS ABB=ON  (WEB2086? OR WEB 2086 OR TNP 470 OR
                TNP470 OR ENDOSTATIN OR SU(W)(5416 OR 6668) OR SU5416 OR
                SU6668 OR BATIM!STAT OR ANGIOSTATIN OR CELECOXIB OR CELEBREX)
L92         549 SEA FILE=WPIDS ABB=ON  (THROMBOCYTE OR PLATELET)(W)ACTIVATING(W
                )(FACTOR# OR SUBSTANCE#)
L93         665 SEA FILE=WPIDS ABB=ON  PAF
L94         527 SEA FILE=WPIDS ABB=ON  (L92 OR L93)(2A)(ANTAGONI? OR INHIBIT?)

L95       58334 SEA FILE=WPIDS ABB=ON  ?CANCER? OR ?NEOPLAS? OR ?LEUKEMI? OR
                ?LEUKAEMI? OR ?CARCINOM? OR ?LYMPHOMA? OR ?SARCOMA? OR
                ?GLIOMA?
L96       42937 SEA FILE=WPIDS ABB=ON  ?TUMOR? OR ?TUMOUR?
L101       3014 SEA FILE=WPIDS ABB=ON  (TUMOR OR TUMOUR)(W)NECROSIS FACTOR#
L102          1 SEA FILE=WPIDS ABB=ON  L94 AND (L95 OR L96) AND L91 NOT L101


=> s l97 or l102

L110          1 L97 OR L102

=> dup rem l107,l018,l106,l109,l110
'L107' IS NOT VALID HERE

=> dup rem l107 l108 l106 l109 l110
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PROCESSING COMPLETED FOR L106
PROCESSING COMPLETED FOR L109
PROCESSING COMPLETED FOR L110
L111          39 DUP REM L107 L108 L106 L109 L110 (11 DUPLICATES REMOVED)
                 ANSWERS '1-17' FROM FILE MEDLINE
                 ANSWERS '18-24' FROM FILE DRUGU
                 ANSWERS '25-32' FROM FILE HCAPLUS
                 ANSWERS '33-39' FROM FILE EMBASE

=> d ibib ab hitrn 1-39; fil hom

L111 ANSWER 1 OF 39      MEDLINE                        DUPLICATE 2
ACCESSION NUMBER:    2002242719      MEDLINE
DOCUMENT NUMBER:     21974862        PubMed ID: 11923217
```

TITLE: Specific PAF antagonist **WEB-2086** induces terminal differentiation of murine and human leukemia cells.
AUTHOR: Cellai Cristina; Laurenzana Anna; Vannucchi Alessandro M; Della Malva Nunzia; Bianchi Lucia; Paoletti Francesco
CORPORATE SOURCE: Department of Experimental Pathology and Oncology, University of Florence, 50134, Firenze, Italy.
SOURCE: FASEB JOURNAL, (2002 May) 16 (7) 733-5.
Journal code: 8804484. ISSN: 1530-6860.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020501
Last Updated on STN: 20030105
Entered Medline: 20020506

AB A pharmacological approach to neoplasia by differentiation therapy relies on the availability of cytodifferentiating agents whose antitumor efficacy is usually assayed first on malignant cells in vitro. Using murine erythroleukemia cells (MELCs) as the model, we found that **WEB-2086**, a triazolobenzodiazepine-derived PAF antagonist originally developed as an anti-inflammatory drug, induces a dose-dependent inhibition of MELC growth and hemoglobin accumulation as a result of a true commitment to differentiation. MELCs treated for 5 days with 1 mM **WEB-2086** show greater than or equal to 85% benzidine-positive cells, increased expression of alpha- and beta-globin genes, and down-regulation of c-Myb. This differentiation pattern, which does not involve histone H4 acetylation and is abrogated by the action of phorbol 12-myristate 13-acetate, recalls the pattern induced by hexamethylene bisacetamide (HMBA). In addition to MELCs, human erythroleukemia K562 and HEL and myeloid HL60 cells are massively committed to maturation by **WEB-2086** and, with some differences, by its analog, WEB-2170. This suggests that **WEB-2086**, structurally distant from other known inducers, might be a member of a new class of cytodifferentiation agents active on a broad range of transformed cells in vitro and useful, prospectively, for anticancer therapy due to their high tolerability in vivo.

L111 ANSWER 2 OF 39 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001514590 MEDLINE
DOCUMENT NUMBER: 21446487 PubMed ID: 11562302
TITLE: Lipid messengers as targets for antiangiogenic therapy.
AUTHOR: Robert E G; Hunt J D
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Louisiana State University Health Sciences Center, New Orleans, Louisiana 70112, USA.. roberte@hhmi.org
SOURCE: CURRENT PHARMACEUTICAL DESIGN, (2001 Nov) 7 (16) 1615-26.
Ref: 103
Journal code: 9602487. ISSN: 1381-6128.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20010920
Last Updated on STN: 20020129
Entered Medline: 20020128

AB Cancer, only second to heart disease, is a leading cause of death in the United States. Despite many years of cancer research little progress has been made in the treatment of many types of cancer. With the advent of

molecular biology and advanced biochemical techniques, we have begun to elucidate the various signaling pathways that account for the transformation of normal cells to malignant cells. Our understanding of cancer cell signaling and cell cycle deregulation has paved the way for the rational design of specific inhibitors. Alas, attempts to specifically and exclusively target treatment to the cancer cell have fallen short of expectations for cure and often result in unfortunate drug side effects. More recently, Folkman proposed neovascularization requirements for tumor expansion and metastasis, and this sparked great interest in both the molecular mechanism of tumor-induced angiogenesis and its potential target for anticancer treatment. In this review, we first describe protein growth factors that have been shown to induce endothelial cell proliferation and angiogenesis. We also discuss the signal transduction cascades that result from growth factor receptor binding in light of drugs that are know to inhibit these cascades. Finally, we discuss the potential use of antagonists of lipid second messengers. In particular BN-50730, a PAF antagonist shows promise in preliminary anti-tumor therapy in vitro and in vivo in athymic nude mice by specifically inhibiting angiogenesis.

L111 ANSWER 3 OF 39 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001041835 MEDLINE
DOCUMENT NUMBER: 20527962 PubMed ID: 11073830
TITLE: PAF produced by human breast cancer cells promotes migration and proliferation of tumor cells and neo-angiogenesis.
AUTHOR: Bussolati B; Biancone L; Cassoni P; Russo S; Rola-Pleszczynski M; Montrucchio G; Camussi G
CORPORATE SOURCE: Department of Internal Medicine, University of Torino, Torino, Italy.
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (2000 Nov) 157 (5) 1713-25. Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001207

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AB Platelet-activating factor (PAF), a phospholipid mediator of inflammation, is present in breast cancer tissue and correlates with microvessel density. In the present study, we investigated the biological significance of PAF synthesized within breast cancer. In vitro, we observed the production of PAF by two estrogen-dependent (MCF7 and T-47D) and an estrogen-independent (MDA-MB231) breast cancer cell lines after stimulation with vascular endothelial growth factor, basic fibroblast growth factor, hepatocyte growth factor, tumor necrosis factor, thrombin but not with estrogen, progesterone, and oxytocin. The sensitivity to agonist stimulation and the amount of PAF synthesized as cell-associated or released varied in different cell lines, being higher in MDA-MB231 cells, which are known to be highly invasive. We further demonstrate, by reverse transcriptase-polymerase chain reaction and cytofluorimetry, that all of the breast cancer cells express the PAF receptor and respond to PAF stimulation in terms of proliferation. Moreover, in MDA-MB231 cells PAF elicited cell motility. In vivo, two structurally different PAF receptor antagonists WEB 2170 and CV 3988 significantly reduced the formation of new vessels in a tumor induced by subcutaneous implantation of MDA-MB231 cells into SCID mice. In conclusion, these results suggest that PAF, produced and released by breast cancer cells, can contribute to tumor development by enhancing cell motility and proliferation and by stimulating the angiogenic response.

L111 ANSWER 4 OF 39 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 93321264 MEDLINE
DOCUMENT NUMBER: 93321264 PubMed ID: 8392443
TITLE: Platelet activating factor, an endogenous mediator of inflammation, induces phenotypic transformation of rat embryo cells.
AUTHOR: Bennett S A; Leite L C; Birnboim H C
CORPORATE SOURCE: Department of Biochemistry, University of Ottawa, Ontario, Canada.
SOURCE: CARCINOGENESIS, (1993 Jul) 14 (7) 1289-96.
Journal code: 8008055. ISSN: 0143-3334.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 19930826
Last Updated on STN: 19930826
Entered Medline: 19930818

AB The ability of platelet activating factor (PAF), a potent endogenous inflammatory agent, to induce phenotypic transformation of primary rat embryo cells (RECs) was investigated. RECs are composed predominantly of fibroblasts, with some epithelial cells and a few neuronal and muscle cells. A 1 h period of treatment with PAF (1 x 10(-8)-1 x 10(-6) M) increased the ability of RECs to (i) form foci, (ii) reach a high saturation density in complete medium, (iii) grow in low serum-containing medium and (iv) exhibit anchorage-independent (AI) growth. Similar changes were achieved with C-PAF (1 x 10(-10)-1 x 10(-8) M), an active, non-metabolizable analog of PAF, but not by lyso-PAF (1 x 10(-10)-1 x 10(-6) M), a biologically inactive metabolite of PAF. All of the PAF-induced phenotypic changes could be inhibited by pretreatment with a PAF receptor antagonist, **CV3988** (1 x 10(-6) M). Pretreatment of RECs with genestein (1 microgram/ml) also completely inhibited all four measures of PAF-induced REC transformation indicating that tyrosine kinase activity may be required for the observed changes in phenotype. Pretreatment with indomethacin (2 x 10(-7) M) blocked the PAF-induced increases in focus formation and saturation density without affecting PAF-induced alterations in growth in low serum or AI growth. This indicates that PAF may exert some of its effects through a cyclooxygenase product. Pretreatment with staurosporine (5 x 10(-8) M) failed to alter any of the PAF-induced effects, suggesting that protein kinase C activity is not involved in REC transformation by PAF. Our results provide the first evidence that PAF, released by activated phagocytes in and around areas of inflammation, may contribute to the process of malignant transformation.

L111 ANSWER 5 OF 39 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 93130501 MEDLINE
DOCUMENT NUMBER: 93130501 PubMed ID: 1483263
TITLE: Lack of therapeutic effects of platelet activating factor antagonists in WEHI-3B leukemia, human xenotransplanted colorectal and lung cancer and Lewis-lung tumor in vivo.
AUTHOR: Koenigsmann M; Zafferani M; Danhauser-Riedl S; Reufi B; Houlihan W J; Thiel E; Berdel W E
CORPORATE SOURCE: Department of Hematology and Oncology, Freie Universitaet Berlin, FRG.
SOURCE: CANCER LETTERS, (1992 Dec 24) 67 (2-3) 145-56.
Journal code: 7600053. ISSN: 0304-3835.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199302

ENTRY DATE: Entered STN: 19930226
Last Updated on STN: 19930226
Entered Medline: 19930218

AB Four new antagonists of platelet activating factor (PAF) from two different chemical classes (imidazoisoquinolines: SDZ 62-434, SDZ 63-135, SDZ 62-759; imidazopiperidines: SDZ 62-293) were tested for in vivo therapeutic activity in various tumor models including the murine myelomonocytic leukemia WEHl-3B, xenografts of human colon (HTB 38) and lung (HTB 119) cancer cell lines and the murine Lewis-lung tumor. After intraperitoneal (i.p.) injection of 1 x 10(3), 5 x 10(3) and 1 x 10(4) WEHl-3B cells into Balb/c mice, the drugs were given per os (p.o.) or i.p. over 6-14 days. Drug doses were pushed to exceed the lethal dose for 10% of the animals (LD10) and ranged from 1 to 100 mg/kg daily for p.o. treatment and from 1 to 75 mg/kg daily for i.p. treatment. In the xenotransplants and the Lewis-lung tumor experiments, PAF antagonists were given i.p. to nude Balb/c and C57 Black mice after intracutaneous (i.c.) tumor cell inoculation. None of the four compounds induced reproducible prolongation of life span, significant numbers of long term survivors, reduction of tumor size, or delay of tumor growth in any of the therapeutic models. Oral SDZ 62-759 had some activity in experiments in which there was slow WEHl-38 tumor growth in the controls. Toxicity of equivalent drugs doses was higher in the i.p. than in the p.o. schedules.

L111 ANSWER 6 OF 39 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 91360612 MEDLINE
DOCUMENT NUMBER: 91360612 PubMed ID: 1886907
TITLE: Effects of the PAF-analog and -antagonist CV-6209 on cultured human glioma cell lines.
AUTHOR: Gati I; Bergstrom M; Muhr C; Carlsson J
CORPORATE SOURCE: Department of Neurology, Akademiska Hospital, Uppsala University, Sweden.
SOURCE: PROSTAGLANDINS LEUKOTRIENES AND ESSENTIAL FATTY ACIDS, (1991 Jun) 43 (2) 103-10.
Journal code: 8802730. ISSN: 0952-3278.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19911027
Last Updated on STN: 19970203
Entered Medline: 19911010

AB Cell lines of human glioma (U-343 MGa and U-251 MG) and human glia (U-533 CG) origin were cultured as monolayers and exposed to CV-6209, an alkyl-phospholipid analog and antagonist of platelet activating factor. This drug had very potent antiproliferative effects on the studied human glioma cell lines; IC50 was 0.9 microM after 48 h treatment and 0.2 microM after 2 weeks treatment. At these doses no growth inhibitory effect was noted on the normal glia cells. The effects on the glioma cells were reversible in the dose intervals, where cell proliferation, 3H-thymidine and 14C-methionine uptakes were greatly inhibited. The simultaneous administration of platelet activating factor [(R)PAF] did not influence the antiproliferative effects of CV-6209 on the cells cultured as monolayers. The structurally similar analog **CV-3988** also had antiproliferative effects, although at 10 times higher concentration than CV-6209. Two other, structurally unrelated, PAF-antagonists (WEB-2086 and TCV-309) gave effects only at very high concentrations. The U-343 MGa cell line was also exposed to CV-6209 when growing as multicellular spheroids. The studies on the spheroid cultures also demonstrated good antitumoral effects with decreases of both the volume growth and the thymidine uptake. The simultaneous administration of (R)PAF reversed the inhibitory effect of CV-6209 on thymidine incorporation. This study demonstrates a strong antitumoral effect at low

concentrations of CV-6209. The antiproliferative effects were probably primarily related to the ether-lipid structure and not to the PAF-antagonistic properties. The good antitumoral effect of CV-6209 on both monolayer and spheroid cultures and the possible PAF-antagonistic properties are discussed.

L111 ANSWER 7 OF 39 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 90153004 MEDLINE
DOCUMENT NUMBER: 90153004 PubMed ID: 2303318
TITLE: Inhibition of Ehrlich ascites tumor in vivo by PAF-antagonists.
AUTHOR: Fecchio D; Russo M; Sirois P; Braquet P; Jancar S
CORPORATE SOURCE: Departamento de Imunologia, Universidade de Sao Paulo, Brazil.
SOURCE: INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, (1990) 12 (1) 57-65.
Journal code: 7904799. ISSN: 0192-0561.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199003
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19900601
Entered Medline: 19900320

AB Several lines of evidence support that PAF modulates the inflammatory and immune responses, and that tumors may inhibit both these processes. In the present study we analysed the effect of PAF antagonists on the growth of Ehrlich Ascites Tumor (EAT) in vivo. Mice were inoculated intraperitoneally with 1 x 10(3) EAT cells and the tumor growth evaluated by counting the number of peritoneal cells, 1,6 and 10 days after tumor implantation. BN 52021 was administered intraperitoneally, intravenously or subcutaneously once or twice a day, at 1.0, 2.5, 5.0 and 20.0 mg/kg. Control animals received 0.1 ml of the vehicle in the same schedule. It was found that i.p. and i.v. administration of BN 52021 (5 mg/kg, twice a day) significantly inhibited EAT growth (80.8% and 56.0% respectively). Other routes and doses were less effective. Another PAF antagonist, SRI 63441 (5 mg/kg, i.p., twice a day) also inhibited EAT growth (80.4%). The BN 52021 added to EAT cells in culture, at concentration of 10(-3) and 10(-4) M, did not affect the viability and proliferation of tumors cells. In an attempt to understand the mechanism of this inhibition, we analyzed the peritoneal macrophages for spreading ability and H2O2 release. It was found that 24 h after tumor implantation there was an increase in the spreading ability of peritoneal macrophages (75%) and that, as the tumor grew, the spreading index fell to control levels (less than 10%). (5 mg/kg/twice a day) the spreading remained elevated (50-60%) at all the times examined. Release of H2O2, measured by horseradish peroxidase-phenol red oxidation, was below detectable levels throughout tumor growth. (ABSTRACT TRUNCATED AT 250 WORDS)

L111 ANSWER 8 OF 39 MEDLINE
ACCESSION NUMBER: 2002494577 MEDLINE
DOCUMENT NUMBER: 22242242 PubMed ID: 12354298
TITLE: Platelet activating factor-induced apoptosis is inhibited by ectopic expression of the platelet activating factor G-protein coupled receptor.
AUTHOR: Brewer Cynthia; Bonin Fanny; Bullock Paula; Nault Marie-Christine; Morin Jennifer; Imbeault Sophie; Shen T Y; Franks D J; Bennett Steffany A L
CORPORATE SOURCE: Neural Regeneration Laboratory, Department of Biochemistry, Microbiology, and Immunology, University of Ottawa, Ottawa, Ontario, Canada.
SOURCE: JOURNAL OF NEUROCHEMISTRY, (2002 Sep) 82 (6) 1502-11.

Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20021002
Last Updated on STN: 20021023
Entered Medline: 20021022

AB The pro-inflammatory lipid mediator platelet activating factor (PAF: 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) accumulates in ischemia, epilepsy, and human immunodeficiency virus-1-associated dementia and is implicated in neuronal loss. The present study was undertaken to establish a role for its G-protein coupled receptor in regulating neurotoxicity. PC12 cells do not express PAF receptor mRNA as demonstrated by northern analysis and RT-PCR. In the absence of the G-protein coupled receptor, PAF (0.1-1 micro m) triggered chromatin condensation, DNA strand breaks, oligonucleosomal fragmentation, and nuclear disintegration characteristic of apoptosis. Lyso-PAF (0.001-1 micro m), the immediate metabolite of PAF, did not elicit apoptotic death. Concentrations of PAF or lyso-PAF that exceeded critical micelle concentration had physicochemical effects on plasma membrane resulting in necrosis. Apoptosis but not necrosis was inhibited by the PAF antagonist BN52021 (1-100 micro m) but not **CV3988** (0.2-20 micro m). Ectopic PAF receptor expression protected PC12 transfectants from ligand-induced apoptosis. PAF receptor-mediated protection was inhibited by **CV3988** (1 micro m). These data provide empirical evidence that: (i) PAF can initiate apoptosis independently of its G-protein coupled receptor; (ii) PAF signaling initiated by its G-protein coupled receptor is cytoprotective to PC12 cells; (iii) the pro- and anti-apoptotic effects of PAF on PC12 cells can be pharmacologically distinguished using two different PAF antagonists.

L111 ANSWER 9 OF 39 MEDLINE
ACCESSION NUMBER: 95250555 MEDLINE
DOCUMENT NUMBER: 95250555 PubMed ID: 7732893
TITLE: Platelet activating factor induces transformation of human fibroblasts.
AUTHOR: Bennett S A; Birnboim H C
CORPORATE SOURCE: Department of Biochemistry, University of Ottawa, Ont., Canada.
SOURCE: ADVANCES IN PROSTAGLANDIN, THROMBOXANE, AND LEUKOTRIENE RESEARCH, (1995) 23 467-9.
Journal code: 8211444. ISSN: 0732-8141.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950608
Last Updated on STN: 19980206
Entered Medline: 19950531

L111 ANSWER 10 OF 39 MEDLINE
ACCESSION NUMBER: 95367474 MEDLINE
DOCUMENT NUMBER: 95367474 PubMed ID: 7640206
TITLE: Growth arrest vs direct cytotoxicity and the importance of molecular structure for the in vitro anti-tumour activity of ether lipids.
AUTHOR: Lohmeyer M; Workman P
CORPORATE SOURCE: MRC Clinical Oncology and Radiotherapeutics Unit, MRC Centre, Cambridge, UK.
SOURCE: BRITISH JOURNAL OF CANCER, (1995 Aug) 72 (2) 277-86.

Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950930
Last Updated on STN: 19980206
Entered Medline: 19950921

AB A panel of 25 different lipid agents was evaluated for in vitro activity against HT29 human colon carcinoma and HL60 promyelocytic leukaemia cells by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The structure-activity relationships seen with this series, including those for four sets of positional or stereoisomers, indicate that specific receptor proteins are unlikely as targets for anti-tumour lipid (ATL) action. Additional data confirm the lack of involvement of the platelet-activating factor receptor in particular and suggest that metabolic stability is a most important determinant of ATL activity. More detailed studies, with 1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocholine (ET18-OCH3) and (+/-)-2-(Hydroxy[tetrahydro-2-(octadecyloxy)methylfuran-2- yl]methoxyphosphinyloxy)-N,N,N,-trimethylethaniminium hydroxide (SRI 62-834), suggest three different modes of activity, depending on drug concentration and exposure time. Low doses of up to 5 microM in standard serum-containing medium cause population growth arrest after prolonged exposure. Growth arrest was associated with a leaky G2/M block as determined by flow cytometry. These effects are reversible. Intermediate concentrations (5-40 microM) were cytotoxic, causing a net reduction in cell numbers after 2-3 days. At even higher concentrations, all lipids caused rapid, direct membrane lysis. When the clonogenic assay was used to assess the effects of ATLs, most agents reduced colony formation at concentrations above 5 microM. However, some compounds proved stimulatory at nanomolar concentrations, suggesting that they might possess mitogenic properties. These results, particularly those concerning the concentration and time dependence, may be relevant to current clinical trials with ether lipids.

L111 ANSWER 11 OF 39 MEDLINE
ACCESSION NUMBER: 95295972 MEDLINE
DOCUMENT NUMBER: 95295972 PubMed ID: 7777190
TITLE: Presence of specific platelet-activating factor binding-sites in neuroblastoma N1E-115 cells.
AUTHOR: Lalouette F; Diserbo M; Martin C; Verdetti J; Fatome M
CORPORATE SOURCE: Unite de Radioprotection Centre de Recherches du Service de Sante des Armees Emile Parde 24, La Tronche, France.
SOURCE: NEUROSCIENCE LETTERS, (1995 Feb 17) 186 (2-3) 173-6.
Journal code: 7600130. ISSN: 0304-3940.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950720
Last Updated on STN: 19970203
Entered Medline: 19950710

AB In this study we reported evidence for the existence of specific binding sites for platelet-activating factor (PAF) in neuroblastoma N1E-115 cells. The specific [3H]PAF binding reached a steady state level within 60 min at 25 degrees C. Scatchard analysis of the specific [3H]PAF binding revealed the presence of two apparent populations of binding sites. The high-affinity binding site possessed a Kd1 of 2.5 +/- 0.6 pM and Bmax1 = 57.3 +/- 20.0 fmol/mg protein. The low-affinity binding site possessed a Kd2 = 3.2 +/- 1.0 nM and Bmax2 = 4.4 +/- 2.1 pmol/mg protein. Furthermore, the total [3H]PAF binding was partially displaced by

unlabelled PAF, PAF antagonists BN 52021 and **BN 50730** in a dose-dependent manner. This study confirms the presence of specific PAF receptors in neuronal cells.

L111 ANSWER 12 OF 39 MEDLINE
ACCESSION NUMBER: 92378790 MEDLINE
DOCUMENT NUMBER: 92378790 PubMed ID: 1324692
TITLE: Two different sites of action for platelet activating factor and 1-O-alkyl-2-O-methyl-sn-glycero-3-phosphocholine on platelets and leukemic cells.
AUTHOR: Salari H; Dryden P; Howard S; Bittman R
CORPORATE SOURCE: Department of Medicine, University of British Columbia, Vancouver, Canada.
CONTRACT NUMBER: HL 16660 (NHLBI)
SOURCE: BIOCHEMISTRY AND CELL BIOLOGY, (1992 Feb) 70 (2) 129-35. Journal code: 8606068. ISSN: 0829-8211.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 19921018
Last Updated on STN: 19970203
Entered Medline: 19920929

AB 2-O-Methyl analogs of platelet activating factor (PAF) are potent anticancer agents. The sites of action and mechanisms of cell toxicity of these agents are as yet unknown. To better understand the mode of action of this class of anticancer agents, we examined the ability of 1-O-hexadecyl-2-acetylglycero-3-phosphocholine with the S or R configuration at C2 ((R)-PAF and (S)-PAF) and 1-O-hexadecyl-2-methoxyglycero-3-phosphocholine with the S or R configuration at C2 ((R)-ET-16-OCH3-GPC and (S)-ET-16-OCH3-GPC) to induce rabbit platelet aggregation and to inhibit [3H]thymidine uptake into WEHI-3B cells, HL-60 cells, and normal blood lymphocytes. The four chiral ether-linked lipids caused aggregation of rabbit platelets with the following order of potency: (R)-PAF greater than (S)-PAF greater than (R)-ET-16-OCH3-GPC greater than (S)-ET-16-OCH3-GPC; the EC50 values were 1 pM, 50 nM, 1 microM, and 50 microM, respectively. The cytotoxic effects of these ether lipids in leukemic cells was in reverse order to that observed for aggregation of platelets. The order of potency for inhibition of [3H]thymidine uptake by WEHI-3B and HL-60 cells was (R)-ET-16-OCH3-GPC = (S)-ET-16-OCH3-GPC greater than (S)-PAF greater than (R)-PAF; the EC50 values were 2, 2, 15, and greater than 40 microM, respectively. PAF antagonists (WEB 2086, **CV 3988**, triazolam, and SRI 63,441) blocked the action of the four ether lipids on platelets, while SRI 63,441 blocked the antineoplastic activity of the ether lipids on WEHI-3B and HL-60 cells. None of the four lipids was able to kill normal lymphocytes significantly. Scatchard analysis of PAF receptor binding revealed that HL-60 and WEHI-3B cells, which are sensitive to the cytotoxic action of ether-linked lipids, do not possess PAF receptors, whereas both normal lymphocytes and platelets do possess a PAF receptor. The present data indicate that the cytotoxic action of antineoplastic ether-linked lipids does not involve the PAF receptor. The protective role of SRI 63,441 in blocking the proaggregatory activity of the ether lipids in rabbit platelets involves PAF receptor, but cytotoxic activity against WEHI-3B and HL-60 cells does not result from its ability to act as a PAF antagonist.

L111 ANSWER 13 OF 39 MEDLINE
ACCESSION NUMBER: 92310169 MEDLINE
DOCUMENT NUMBER: 92310169 PubMed ID: 1819710
TITLE: Calcium ion mobilization in neuronal cells induced by PAF.
AUTHOR: Kornecki E; Ehrlich Y H

CORPORATE SOURCE: Department of Anatomy and Cell Biology, State University of New York Health Science Center, Brooklyn 11203.
SOURCE: LIPIDS, (1991 Dec) 26 (12) 1243-6.
Journal code: 0060450. ISSN: 0024-4201.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920807
Last Updated on STN: 19970203
Entered Medline: 19920730

AB We have reported previously that platelet-activating factor (PAF) interacts with the neuronal cell line NG108-15 (neuroblastoma X glioma hybrid) and the pheochromocytoma cell line, PC12. PAF acts on these cells by raising levels of intracellular free calcium ions. In the present report, we extend these studies. PAF induced the vesicular release of adenosine 5'-triphosphate (ATP) from PC12 cells in a dose-dependent manner. The PAF-induced ATP release was inhibited by the PAF antagonists, **CV-3988** and CV-6209, and the calcium antagonist prenylamine. The relevance of the interaction of PAF with neuronal cells was investigated further by using brain synaptosomal preparations and primary cortical and neostriatal cells. Nanomolar concentrations of PAF induced calcium transients in aequorin-loaded synaptosomal preparations, and cortical and neostriatal cells were sensitive to the action of PAF. The possible physiological and pathophysiological roles of PAF in brain function are discussed.

L111 ANSWER 14 OF 39 MEDLINE
ACCESSION NUMBER: 91070495 MEDLINE
DOCUMENT NUMBER: 91070495 PubMed ID: 2253199
TITLE: Role of endocytosis in the action of ether lipids on WEHI-3B, HL60, and FDCP-mix A4 cells.
AUTHOR: Bazill G W; Dexter T M
CORPORATE SOURCE: Department of Experimental Haematology, Paterson Institute for Cancer Research, Christie Hospital, Manchester, United Kingdom.
SOURCE: CANCER RESEARCH, (1990 Dec 1) 50 (23) 7505-12.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 19910308
Last Updated on STN: 19910308
Entered Medline: 19910122

AB We investigated the effect of a number of platelet activating factor antagonists on cell killing by 1-O-octadecyl-2-O-methyl-sn-glycero-3-phosphoryl choline (ET-18-OCH3). Of six platelet activating factor antagonists tested, four were found to protect WEHI-3B leukemic cells against cell death induced by ET-18-OCH3. Certain other compounds, not platelet activating factor antagonists, had similar protective effects. The protective compounds were all lipophilic weak bases. We describe experiments that indicate that these compounds protect by inhibition of endocytic uptake of ET-18-OCH3. Sensitive cells showed rapid endocytic uptake, whereas in resistant cells, uptake was slow. Uptake of ET-18-OCH3 could be suppressed by inhibitors of endocytosis such as chloroquine, monensin, and vinblastine. We conclude that one of the principal determinants of sensitivity or resistance to ether lipids may be the rate at which cells take them up by endocytosis.

L111 ANSWER 15 OF 39 MEDLINE

ACCESSION NUMBER: 90063064 MEDLINE
DOCUMENT NUMBER: 90063064 PubMed ID: 2555416
TITLE: Identification of functional platelet-activating factor receptors in Raji lymphoblasts.
AUTHOR: Travers J B; Li Q; Kniss D A; Fertel R H
CORPORATE SOURCE: Department of Pharmacology, Ohio State University College of Medicine, Columbus 43210.
SOURCE: JOURNAL OF IMMUNOLOGY, (1989 Dec 1) 143 (11) 3708-13.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199001
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19980206
Entered Medline: 19900105

AB The binding and metabolism of platelet-activating factor (PAF) were characterized in Raji, a human Burkitt's lymphoma-derived cell line. Raji lymphoblasts readily metabolized PAF by deacetylation-reacylation at 37 degrees C, but not at 4 degrees C. Binding studies conducted at 4 degrees C demonstrated specific binding that reached saturation within 80 min. This binding was only partially reversible. Scatchard analysis of PAF binding data revealed a single class of PAF binding sites (17,800 +/- 3,600/cell) with a K of 2.3 +/- 0.3 nM. These high-affinity PAF binding sites were shown to be functional receptors, as 100 pM to 1 microM PAF increased free intracellular calcium in a dose-dependent manner. The dose of PAF necessary to achieve half maximal calcium mobilization response was 6.3 nM, which was in the range of the K for the receptor calculated from the binding studies. The structurally dissimilar PAF receptor antagonists **CV-3988** and BN52021 inhibited the PAF-induced calcium changes at doses that competed with PAF binding. These studies provide the first evidence for a functional PAF receptor expressed on a lymphocyte cell line.

L111 ANSWER 16 OF 39 MEDLINE
ACCESSION NUMBER: 88260551 MEDLINE
DOCUMENT NUMBER: 88260551 PubMed ID: 2898694
TITLE: Treatment of adult systemic mastocytosis with a PAF-acether antagonist BN52063.
AUTHOR: Guinot P; Summerhayes C; Berdah L; Duchier J; Revillaud R J
SOURCE: LANCET, (1988 Jul 9) 2 (8602) 114.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198808
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19950206
Entered Medline: 19880811

L111 ANSWER 17 OF 39 MEDLINE
ACCESSION NUMBER: 89023522 MEDLINE
DOCUMENT NUMBER: 89023522 PubMed ID: 3177629
TITLE: Platelet activating factor induces dopamine release in PC-12 cell line.
AUTHOR: Bussolino F; Tessari F; Turrini F; Braquet P; Camussi G; Prosdocimi M; Bosia A
CORPORATE SOURCE: Dipartimento di Genetica, Biologia e Chimica Medica, Universita di Torino, Italy.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1988 Oct) 255 (4 Pt 1) C559-65.

Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198811
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881110

AB The ability of platelet activating factor (PAF) to stimulate dopamine release and modify calcium homeostasis in PC-12 cell line was studied. PAF-induced dopamine release is related to its molecular form, with only the R-form steric configuration [(R)PAF], but not its S-form or its 2-lyso derivative, effective at being active. In addition, PAF acts at very low concentrations in a dose-dependent manner (0.1-30 nM). Preincubation with PAF receptor antagonists (**CV-3988** and BN52021) as well as the specific desensitization of PC-12 cells to (R)PAF abolish the (R)PAF-induced dopamine release. Several lines of evidence suggest that dopamine release is dependent on a (R)PAF-induced calcium influx and efflux modulation. Dopamine release by PC-12 cells challenged with (R)PAF is associated with a rapid 45Ca influx and efflux and a rise in cytoplasmic calcium concentrations ([Ca2+]i) evaluated by using the calcium indicators fura-2 and quin2. At 30 nM (R)PAF, the absence of extracellular calcium inhibits the dopamine release but not the rise of [Ca2+]i from the internal stores, suggesting the importance of calcium influx in (R)PAF-induced dopamine release. PAF, which has been reported to be synthesized by stimulated neuronal cells (J. Biol. Chem. 261: 16502-16508, 1986) may thus have a physiological modulatory role on cells with neurosecretory properties.

L111 ANSWER 18 OF 39 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1995-45852 DRUGU M P
TITLE: Streptococcus pneumoniae anchor to activated human cells by the receptor for platelet activating factor.
AUTHOR: Cundell D R; Gerard N P; Gerard C; Idanpaan-Heikkila I; Tuomanen E I
CORPORATE SOURCE: Univ.Rockerfeller; Univ.Harvard
LOCATION: New York, N.Y.; Boston., Mass., USA
SOURCE: Nature (377, No. 6548, 435-38, 1995) 3 Fig. 1 Tab. 30 Ref.
CODEN: NATUAS ISSN: 0028-0836
AVAIL. OF DOC.: Laboratory of Molecular Infectious Diseases, Rockerfeller University, New York, New York 10021-6399, U.S.A. (E.I.T.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AB L-659989 (Merck-USA) attenuated the internalization of Strept. pneumoniae into isolated human umbilical vein endothelial cells which had been activated with tumor necrosis-factor-alpha (TNF-a, Boehr.Mannheim), thrombin (Sigma-Chem.) or interleukin-1-alpha (IL-1a, Boehr.Mannheim). L-659989 and **WEB-2086** (apafant, Boehr.Mannheim) prevented the adherence of bacteria to COS-7 cells which were transfected with human PAF-receptor complementary DNA. Intratracheal or intranasal L-659989 attenuated the nasal colonization of Strept. pneumoniae and the progression to full pneumonia in rabbits treated with interleukin-1 (IL-1). Gentamicin was used. Presentation of the PAF receptor during inflammatory activation of host cells is critical to the biology of pneumococcal infection.

L111 ANSWER 19 OF 39 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1993-28254 DRUGU B P
TITLE: In Vitro Antitumour Activity of the Novel Imidazoisoquinoline SDZ 62-434.

AUTHOR: Brunton V G; Workman P
LOCATION: Glasgow, United Kingdom
SOURCE: Br.J.Cancer (67, No. 5, 989-95, 1993) 8 Fig. 2 Tab. 30 Ref.
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Cancer Research Campaign Laboratories, CRC Department of Medical Oncology, University of Glasgow, Garscube Estate, Switchback Road, Bearsden, Glasgow, G61 1 BD, Scotland.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB In a range of cell-lines from human solid and hematological malignancies there was a wide range of sensitivities to SDZ-62-434 diHCl (Sandoz), which was more active in the hematological cell-lines than in many of the solid tumors, as measured by a cytotoxicity assay. Of these it was most active in 2 colon adenocarcinoma cell-lines and in tumor lines of CNS origin. The most resistant line was a breast adenocarcinoma. SDZ-62-434 dose-dependently inhibited cell growth in an ovarian adenocarcinoma cell-line, and was not affected by pretreatment with WEB-2086 (apafant, Boehr.Ingelheim). In a murine cell-line SDZ-62-434 inhibited DNA synthesis induced by platelet-derived growth factor (PDGF, Boehr.Mannheim) or bombesin (BM, Sigma-Chem.).

L111 ANSWER 20 OF 39 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1991-40772 DRUGU P
TITLE: SDZ 62-434, a Novel Imidazo (2,1-a)isoquinoline **PAF** Receptor Antagonist with In-Vitro and In-Vivo Antitumor Activity.
AUTHOR: Houlihan W J; Munder P G; Berdel W E; Nemecek G M; Schmitt G; Winslow C M
CORPORATE SOURCE: Sandoz
LOCATION: East Hanover, New Jersey, United States; Freiburg, Berlin, Germany,West
SOURCE: Proc.Am.Assoc.Cancer Res. (32, 82 Meet., 407, 1991) 1 Ref.
ISSN: 0197-016X
AVAIL. OF DOC.: Sandoz Research Institute, Route 10, East Hanover, NJ 07936, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Using the PAF molecule as a template, a novel class of non-charged PAF receptor antagonist was designed containing the imidazo (2,1-a)isoquinoline nucleus. This class differs from other non-charged PAF antagonists in that they possess antitumor activity in the range of the clinically active ET-18-OCH3. 1 Member of this series, 5-(4'-piperidinomethyl- phenyl-2,3-dihydroimidazo (2,1-a)isoquinoline dihydrochloride (SDZ-62-434) demonstrated strong direct and macrophage induced cytoxicity against a variety of murine lymphomas and leukemias and cytostatic/ antiproliferative activity against human colorectal, colon and kidney tumor cell lines. In the 28 day mouse MethA fibrosarcoma model, SDZ-62-434 gave a PD50 against death of 0.025 mg/kg p.o. (LD50 = 300 mg/kg p.o.). (congress abstract).

L111 ANSWER 21 OF 39 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1991-31825 DRUGU P
TITLE: Platelet-Activating Factor (**PAF**) Receptor-Mediated Calcium Mobilization and Phosphoinositide Turnover in Neurohybrid NG108-15 Cells: Studies with BN50739, a New **PAF** Antagonist.
AUTHOR: Yue T; Gleason M M; Gu J L; Lysko P G; Hallenbeck J; Feuerstein G
CORPORATE SOURCE: SK-Beecham

LOCATION: King of Prussia, Pennsylvania, Bethesda, Maryland, United States
SOURCE: J.Pharmacol.Exp.Ther. (257, No. 1, 374-81, 1991) 10 Fig. 2 Tab. 56 Ref.
CODEN: JPETAB ISSN: 0022-3565
AVAIL. OF DOC.: Department of Pharmacology, SmithKline Beecham, L-510, P.O. Box 1539, King of Prussia, PA 19406-0939, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB BN-50739, **WEB-2086** (Boehr.Ingelheim), SRI-63-441 (Sandoz), and BN-52021 (ginkgolide-B) but not nifedipine (NF) and diltiazem (DZX, both Sigma-Chem.), dose-dependently antagonized the PAF-induced increase in (Ca++)i in hybrid NG108-15 cells obtained from parent mouse neuroblastoma cells (N18TG2) and rat glioma cells (C6-BU-1). Norepinephrine (noradrenaline), clonidine, phenylephrine, methoxyamine, isoproferenol (isoprenaline) and epinephrine (adrenaline), glutamate, neuropeptide Y, cAMP, carbachol, LTB4, LTD4 and U-46619 were ineffective. The response of NG108-15 cells to PAF involves activation of phospholipase C and increases in (Ca++)i via specific PAF receptors.

L111 ANSWER 22 OF 39 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1991-14216 DRUGU P
TITLE: Some Antagonists of Platelet Activating Factor are Cytotoxic for Human Malignant Cell Lines.
AUTHOR: Danhauser Riedl S; Felix S B; Houlihan W J; Zafferani M; Steinhauser G; Oberberg D
CORPORATE SOURCE: Sandoz
LOCATION: Munich, Germany,West; East Hanover, New Jersey, United States
SOURCE: Cancer Res. (51, No. 1, 43-48, 1991) 4 Fig. 4 Tab. 22 Ref.
CODEN: CNREA8 ISSN: 0008-5472
AVAIL. OF DOC.: Department of Hematology and Oncology, Klinikum Steglitz, Freie Universitaet, Berlin, Hindenburgdamm 30, 1000 Berlin 45, Germany. (Berdel W E, 10 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature
AB SDZ-62-293 showed the best antineoplastic properties of 9 new PAF-antagonists: imidazoisoquinolines SDZ-62-434, 62-759, 63-135 and 63-596, imidazopiperidines SDZ-61-638, 62-293 and 62-694, the thiopyrimidine (TP) SDZ-59-015, and the thioimidazoline (TI) SDZ-61-813 (all Sandoz). SDZ-63-135 and 62-293 suppressed colony formation in a human tumor cloning assay (HTCA). There was no correlation between antiproliferative activity and PAF-induced human platelet aggregation IC50 values. The antiproliferative activity of SDZ-62-293 was not antagonized by preincubation with **WEB-2086**, WEB-2170 (both Boehr.Ingelheim) or PAF (Berchtold). Studies with **CV-3988** (Takeda) and **WEB-2086** showed no 3H-PAF specific binding sites on 2 cell lines sensitive to the PAF antagonists.

L111 ANSWER 23 OF 39 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1988-31975 DRUGU P
TITLE: Neuroregulatory and Neuropathological Actions of the Ether-Phospholipid Platelet-Activating Factor.
AUTHOR: Kornecki E; Ehrlich Y H
LOCATION: Burlington, Vermont, United States
SOURCE: Science (240, No. 4860, 1792-94, 1988) 3 Fig. 1 Tab. 20 Ref.
CODEN: SCIEAS ISSN: 0036-8075
AVAIL. OF DOC.: Department of Anatomy and Cell Biology, SUNY Health Science Center at Brooklyn, Box 5, Brooklyn, NY 11203, U.S.A.
LANGUAGE: English

DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Platelet activating factor (PAF) increased the intracellular levels of free Ca and released ATP in the clones NG108-15 and PC12. The increase was dependent on intracellular Ca and was inhibited by **CV-3988**, prenylamine and diltiazem; triazolam, alprazolam, nitrendipine and brotizolam had only minimal effects. Exposure of NG108-15 for 3-4 days to low concentrations induced neuronal differentiation; higher concentrations were neurotoxic. PAF may play a physiological role in neuronal development and a pathophysiological role in the degeneration that occurs when neurons are exposed to circulatory factors as a result of trauma, stroke or spinal cord injury.

L111 ANSWER 24 OF 39 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1986-36829 DRUGU B C E
TITLE: Platelet Activating Factor - A Physiologically Active Etherlipid.
AUTHOR: Weber N
LOCATION: Munster, Germany,West
SOURCE: Pharm.Unserer Zeit (15, No. 4, 107-12, 1986) 7 Fig. 23 Ref.
CODEN: PHUZBI ISSN: 0048-3664
AVAIL. OF DOC.: Bundesanstalt fuer Fettforschung, Piusallee 68-76, 4400 Muenster, W. Germany.
LANGUAGE: German
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The role of platelet activating factor (PAF) is reviewed with particular reference to its physiological action and biochemical effects. Its biosynthesis and metabolism are outlined, together with problems involved in the chemical synthesis of PAF. Possible future uses of PAF, its derivatives, and antagonists are discussed.

L111 ANSWER 25 OF 39 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:869581 HCAPLUS
DOCUMENT NUMBER: 137:346168
TITLE: **Platelet-activating factor antagonist inhibition** of **angiogenesis** and tumor growth induced by **basic fibroblast growth factor**
INVENTOR(S): Hunt, Jay D.; Bazan, Haydee E.; Marcheselli, Victor L.; Builla, Gomez Julio Alvarez; Bazan, Nicholas G.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002169158	A1	20021114	US 2002-82821	20020225

PRIORITY APPLN. INFO.: US 2001-271285P P 20010223
AB A novel use of platelet-activating factor antagonists that bind to intracellular PAF binding sites such as **BN-50730** (tetrahedra-4,7,8,10 methyl-1 (chloro-1 phenyl)-6 (methoxy-4 phenyl-carbamoyl)-9 pyrido [4',3'-4,5] thieno [3,2-f] triazolo-1,2,4 [4,3-a] diazepine-1,4) has been discovered. These intracellular-binding platelet-activating factor antagonists were found to inhibit both in vivo and in vitro tumor growth and **angiogenesis** where the

angiogenesis is stimulated by **basic fibroblast growth factor**. **BN-50730** significantly reduced the size of s.c. and intrathoracic human tumor xenografts in nude mice. The in vivo decrease in tumor growth was due to an **antiangiogenic** effect.

IT **86090-08-6, Angiostatin 105219-56-5, WEB 2086 129298-91-5, TNP-470 130370-60-4, Batimastat 169590-42-5, Celecoxib 187888-07-9, Endostatin 204005-46-9, SU 5416 252916-29-3, SU 6668**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as addnl. agent **inhibiting** tumor **angiogenesis**; **platelet-activating factor antagonist inhibition** of **angiogenesis** and tumor growth induced by **basic fibroblast growth factor**)

IT **65154-06-5, Platelet-activating factor**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**platelet-activating factor antagonist inhibition** of **angiogenesis** and tumor growth induced by **basic fibroblast growth factor**)

IT **85703-73-7, CV 3988 132579-32-9, BN-50730**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**platelet-activating factor antagonist inhibition** of **angiogenesis** and tumor growth induced by **basic fibroblast growth factor**)

L111 ANSWER 26 OF 39 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 5
ACCESSION NUMBER: 1999:786131 HCAPLUS
DOCUMENT NUMBER: 132:263973
TITLE: Motility induced by human immunodeficiency virus-1 tat on Kaposi's sarcoma cells requires platelet-activating factor synthesis
AUTHOR(S): Biancone, Luigi; Cantaluppi, Vincenzo; Boccellino, Mariarosaria; Bussolati, Benedetta; Del Sorbo, Lorenzo; Conaldi, Pier Giulio; Albini, Adriana; Toniolo, Antonio; Camussi, Giovanni
CORPORATE SOURCE: Cattedra di Nefrologia, Universita di Torino, Turin, 10126, Italy
SOURCE: American Journal of Pathology (1999), 155(5), 1731-1739
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present study, we evaluated whether motility of Kaposi's sarcoma (KS) spindle cells induced by HIV-1 Tat protein is dependent on the synthesis of platelet-activating factor (PAF). The results obtained indicate that Tat induced a dose-dependent synthesis of PAF from KS cells at a concn. as low as 0.1 ng/mL. PAF prodn. started rapidly after Tat stimulation, peaking at 30 min and declining thereafter. Tat-induced cell migration was also a rapid event starting at 30 min. The motility was abrogated by addn. of a panel of chem. unrelated PAF receptor antagonists (WEB 2170, CV 3988, CV 6209, and BN 52021), suggesting that the synthesized PAF mediates the mitogenic effect of Tat. This effect was also present on cells plated on a type-I collagen-, fibronectin-, or basement membrane ext.-coated surface. Expression of PAF

receptor-specific mRNA was detected in KS cells. In addn., examn. of the cytoskeletal organization showed that Tat-mediated KS cell redistribution of actin filaments and shape change was also inhibited by a PAF receptor antagonist. Moreover, PAF receptor blockade prevented the up-regulation of .beta.1 integrin and the down-regulation of .alpha.v.beta.3 obsd. after stimulation of KS cells with Tat. In conclusion, the results of the present study indicate that Tat-induced PAF synthesis plays a crit. role in triggering the events involved in motility of KS cells.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L111 ANSWER 27 OF 39 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 6
ACCESSION NUMBER: 1998:20354 HCAPLUS
DOCUMENT NUMBER: 128:165462
TITLE: Receptor-mediated and protein kinase-dependent growth enhancement of primary human fibroblasts by platelet activating factor
AUTHOR(S): Bennett, Steffany A. L.; Birnboim, H. Chaim
CORPORATE SOURCE: Ottawa Regional Cancer Centre and Department of Biochemistry, University of Ottawa, Ottawa, ON, K1H 8L6, Can.
SOURCE: Molecular Carcinogenesis (1997), 20(4), 366-375
CODEN: MOCAE8; ISSN: 0899-1987
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chronic inflammation is a recognized risk factor for human cancer, but the causal mechanisms are poorly understood. We previously demonstrated that platelet activating factor (PAF) can induce alterations in the in vitro growth properties of primary rat fibroblasts. In the study reported here, exposure of primary human skin fibroblasts to PAF for 1 h in serum-free medium was shown to cause sustained proliferation over 50 d in medium contg. low serum and anchorage-independent growth in soft agarose. Both properties could be inhibited by pretreatment with a PAF receptor antagonist, **CV3988** (10 .mu.M); a tyrosine-kinase inhibitor, genistein (1 .mu.g/mL); or a protein kinase C (PKC) inhibitor, staurosporine (50 nM) but not with a cyclooxygenase inhibitor, indomethacin (200 nM-20 .mu.M). PAF had no effect on doubling time, satn. d., or cell viability under normal monolayer growth conditions in complete medium. Treatment with lyso-PAF, an inactive metabolite of PAF, had no effect in either of the assays. Control and PAF-induced cell proliferation in low-serum medium was inhibited by PAF receptor antagonists present during the extended growth period. The presence of PAF receptor mRNA in human skin fibroblasts was demonstrated by reverse transcriptase-polymerase chain reaction. The presence of a functional receptor was indicated by an early (2 min) transient increase in PKC activity and an increase in fos mRNA after PAF treatment. PAF-induced PKC activity was blocked by pretreatment with either staurosporine (50 nM) or **CV3988** (1 .mu.M). These results suggest that PAF is a mitogenic factor that contributes to the known increase in risk of malignancy assocd. with chronic inflammatory conditions.

L111 ANSWER 28 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:356269 HCAPLUS
TITLE: Type 4 phosphodiesterase inhibitors and therapeutic uses thereof
INVENTOR(S): Eggenweiler, Hans-Michael; Wolf, Michael
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003037349	A1	20030508	WO 2002-EP9596	20020828

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2001-125394 A 20011031

AB The invention discloses the use of type 4 phosphodiesterase inhibitors (PDE IV inhibitors) to treat diseases, as well as combinations of PDE IV inhibitors with other drugs.

IT INDEXING IN PROGRESS

IT **65154-06-5, Platelet-activating factor**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**antagonists**; phosphodiesterase IV **inhibitors**, therapeutic uses, and use with other agents)

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L111 ANSWER 29 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:591707 HCAPLUS
DOCUMENT NUMBER: 137:140509
TITLE: Preparation of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isozymes
INVENTOR(S): Chambers, Robert J.; Magee, Thomas V.; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 180 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1229034	A1	20020807	EP 2002-250202	20020111

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

US 2002111495	A1	20020815	US 2002-62811	20020131
BR 2002000250	A	20021008	BR 2002-250	20020131

PRIORITY APPLN. INFO.: US 2001-265240P P 20010131
US 1997-43403P P 19970404
US 1998-105120P P 19981021

OTHER SOURCE(S): MARPAT 137:140509

AB Title compds. [I; p, q = 0, 1; m = 0-2; n = 1, 2; A = CO2R7, CONR9CO2R7, CONR7R9, OP(O)(OH)2, SO3H, acylsulfonamido, etc.; W = O, S, SO, SO2, NR3; Y = N, NO, CR11; R1, R2 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, etc.; R3 = H, alkyl, Ph, PhCH2, etc.; R4-R6 = H, F, Cl, alkynyl, cyano, NO2, etc.; R7 = H, (substituted) alkyl, alkenyl, alkynyl; R9 = H, alkyl, cycloalkyl, Ph, PhCH2, pyridyl, etc.; R11 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, fluoroalkoxy, etc.; Ra, Rb = H, F, CF3, alkyl, (substituted) cycloalkyl, Ph, PhCH2; B1, B2 = 3-7 membered (hetero)cyclyl, 7-12 membered poly(hetero)cyclyl; pairs of variables may form rings; with provisos], were prepd. (no data). Thus, Me

2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionate was suspended in Me_3COH. Aq. NaOH was added to the suspension, and the reaction mixt. was refluxed 1 h to give 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionic acid.

IT **65154-06-5, Platelet activating factor**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (**antagonists**, combination therapy; prepn. of nicotinamides and mimetics as **inhibitors** of phosphodiesterase IV isoenzymes)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L111 ANSWER 30 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:351380 HCAPLUS
DOCUMENT NUMBER: 133:825
TITLE: Peptides having anticancer, antiinflammatory, and **angiogenesis**-inhibiting activity
INVENTOR(S): Collin, Peter Donald
PATENT ASSIGNEE(S): Coastside Bio Resources, USA
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000029009	A1	20000525	WO 1999-US27289	19991118

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-109139P P 19981118
US 1999-157078P P 19991001

OTHER SOURCE(S): MARPAT 133:825

AB A pentapeptide is disclosed having the generic formula A-A-A-B-C (A = nonpolar amino acid; B = polar amino acid; C = charged amino acid). In a preferred embodiment, the peptide has the sequence A-Pro-Pro-B-C, and in a further preferred embodiment has the sequence of Leu-Pro-Pro-Ser-Arg. In a most preferred embodiment, the peptide comprises at least one D-amino acid. The peptide can be extd. from the epidermis of sea cucumbers. The peptides of the invention are useful for inhibition of tumor progression and/or inflammation in a mammal by administration of 1-5000 mg/kg body wt. The peptide can be administered in conjunction with any suitable carriers or excipients as are known those skilled in the arts via oral delivery forms, e.g. capsules, drinks, powders, rectally via suppositories, or other suitable means.

IT **65154-06-5, Platelet-activating factor**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (peptides having anticancer, antiinflammatory, and **angiogenesis -inhibiting** activity)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L111 ANSWER 31 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:736476 HCAPLUS

DOCUMENT NUMBER: 131:346535
TITLE: Use of neomycin for treating **angiogenesis** -related diseases
INVENTOR(S): Hu, Guo-Fu; Vallee, Bert L.
PATENT ASSIGNEE(S): The Endowment for Research In Human Biology, Inc., USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958126	A1	19991118	WO 1999-US10269	19990511
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2331620	AA	19991118	CA 1999-2331620	19990511
AU 9939804	A1	19991129	AU 1999-39804	19990511
EP 1083896	A1	20010321	EP 1999-922915	19990511
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6482802	B1	20021119	US 2000-700436	20001109

PRIORITY APPLN. INFO.: US 1998-84921P P 19980511
WO 1999-US10269 W 19990511

AB The present invention is directed to using neomycin or an analog thereof as a therapeutic agent to treat **angiogenesis**-related diseases, which are characterized by excessive, undesired or inappropriate **angiogenesis** or proliferation of endothelial cells. The present invention is also directed to pharmaceutical compns. comprising: (a) neomycin or an analog and, optionally, (b) another anti-**angiogenic** agent or an anti-neoplastic agent. The present invention is further directed to a method for screening neomycin analogs having anti-**angiogenic** activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases. A dose of 20 ng neomycin/embryo or higher completely inhibited **angiogenin** -induced **angiogenesis** in the chorioallantoic membrane (CAM) assay. Neomycin inhibits **angiogenin**-induced **angiogenesis** mainly through inhibition of nuclear translocation of **angiogenin**.

IT **65154-06-5, Platelet activating factor**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(neomycin and analogs are **inhibitors** of nuclear translocation of **angiogenic** factors for treatment of **angiogenesis** -related diseases)

IT **86090-08-6, Angiostatin 129298-91-5,** AGM 1470 **130370-60-4, Batimastat 187888-07-9, Endostatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neomycin, its analogs and other agents for treatment of **angiogenesis**-related diseases)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L111 ANSWER 32 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:169163 HCAPLUS
DOCUMENT NUMBER: 126:207538
TITLE: Treatment of skin diseases using ginkgolide PAF antagonists
INVENTOR(S): Korth, Ruth
PATENT ASSIGNEE(S): Korth, Ruth, Germany
SOURCE: U.S., 12 pp., Cont.-in-part of U.S. 5,346,894.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5605927	A	19970225	US 1994-261765	19940617
EP 540767	A1	19930512	EP 1991-118745	19911104
EP 540767	B1	20020807		
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL, SE				
US 5346894	A	19940913	US 1992-969674	19921028
US 5696114	A	19971209	US 1994-246476	19940519
US 5852052	A	19981222	US 1996-761938	19961209
US 5895785	A	19990420	US 1997-938357	19970929
US 2002127287	A1	20020912	US 2001-21005	20011219

PRIORITY APPLN. INFO.:

EP 1991-118745	A	19911104
US 1992-969674	A1	19921028
US 1994-246476	B2	19940519
DE 1987-3735525	A	19871020
DE 1990-4017818	A	19900601
DE 1990-4034090	A	19901026
US 1991-704554	B3	19910523
EP 1991-118744	A	19911104
US 1992-844882	B1	19920303
US 1992-845088	A2	19920303
US 1992-968878	B1	19921030
US 1992-994752	B2	19921222
DE 1992-4244265	A	19921228
US 1993-104599	A2	19930811
US 1993-172234	A2	19931223
US 1994-261765	A3	19940617
US 1995-444103	B1	19950518
US 1996-761938	A3	19961209
US 1998-136757	B2	19980819
US 1999-435859	B1	19991108

AB The invention refers to the treatment and prevention of lyso-PAF-mediated skin disorders with an effective amt. of at least one antagonist against lyso-PAF receptors. Lyso-PAF or PAF receptor antagonists were administered with or without an antagonist against prodn. of ether phospholipids. Lyso-PAF antagonists of the invention are natural ginkgolides, i.e. BN 52020, BN 52021, BN 52022 and mixts. thereof, which are administered, for example, by food or topically. Examples dealing with lyso-PAF in cerebrospinal fluid of patients with mental and inflammatory disorders and PAF receptors and lyso-PAF receptors on leukocytes were presented.

IT **85703-73-7**, **CV 3988** **105219-56-5**, **WEB 2086**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonists of ether-contg. phospholipids for treatment of leukocyte- or PAF-mediated diseases)

IT **65154-06-5**, **Platelet-activating factor**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(receptors for; **antagonists** of ether-contg. phospholipids for
treatment of leukocyte- or PAF-mediated diseases)

L111 ANSWER 33 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002192587 EMBASE
TITLE: Non-haematological functions of platelets.
AUTHOR: Mukhopadhyay S.; Mukhopadhyay A.K.
CORPORATE SOURCE: S. Mukhopadhyay, All India Inst. of Medical Sciences, Department of Laboratory Medicine, Ansari Nagar, New Delhi 110029, India. mukhoak@medinst.ernet.in
SOURCE: National Medical Journal of India, (2002) 15/2 (78-83).
Refs: 80
ISSN: 0970-258X CODEN: NMJIEU
COUNTRY: India
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
LANGUAGE: English

L111 ANSWER 34 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96280451 EMBASE
DOCUMENT NUMBER: 1996280451
TITLE: Bleomycin antibiotics and their role in cancer chemotherapy.
AUTHOR: Huang L.; Xie Y.; Lown J.W.
CORPORATE SOURCE: Department of Chemistry, University of Alberta,Edmonton, Alta. T6G 2G2, Canada
SOURCE: Expert Opinion on Therapeutic Patents, (1996) 6/9 (893-899).
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
052 Toxicology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The bleomycins are a group of glycopeptide anticancer cytotoxic agents which have been used in the clinical treatment of several human malignancies as single or combination chemotherapy for over two decades. However, the risk of dose-dependent pulmonary toxicity, which ultimately results in pulmonary fibrosis, limits the scale of application. Meanwhile, the unique mechanism of the antitumour effects of bleomycins has also attracted considerable interest from biologists. Extensive studies at the molecular level have provided a guide to attempts to obviate the pulmonary toxicity. Recent progress made in the areas of drug delivery, electropermeabilisation and conjugate synthesis has provided valuable additional information to improve bleomycin chemotherapy. The patents and publications discussed in this review are selected from those covering the period from 1992 to date based on a Chemical Abstracts search.

L111 ANSWER 35 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93119582 EMBASE
DOCUMENT NUMBER: 1993119582
TITLE: Platelet-activating factor antagonists (BN 52021 and

BN 50730) inhibit tumor necrosis factor-alfa-mediated cytotoxicity on murine L929 tumor cells.
AUTHOR: Hunyadi J.; Kenderessy A.S.; Duba E.; Braquet P.; Dobozy A.
CORPORATE SOURCE: Department of Dermatology, Albert Szent-Gyorgyi Medical Univ., P.O. Box 480,Szeged, Hungary
SOURCE: Molecular Immunology, (1993) 30/6 (517-519).
ISSN: 0161-5890 CODEN: IMCHAZ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Tumor necrosis factor (TNF)-alfa has been described as a mononuclear phagocyte-produced cytotoxin that causes the necrosis and regression of some tumors. The mechanism of the cytotoxicity and the basis for the differential cytotoxic effects of TNF against cells of various origin remains unclear. It has also been reported, that murine TNF stimulates the production of platelet-activating factor (PAF) by cultured peritoneal macrophages, and that PAF enhances TNF production by alveolar macrophages. Furthermore, it is known that the synthesis and release of PAF are inhibited by plasma proteinase inhibitors. This study was devoted to investigate the effects of two specific PAF antagonists (BN 52021 and 50730), and a proteinase inhibitor (aprotinin; Gordox(R)) on the TNF-induced cytotoxicity in L929 murine fibroblasts. Our present findings indicate that TNF-induced cytotoxicity is inhibited in a dose-dependent manner by the PAF antagonists studied and by the kallikrein inhibitor aprotinin. These findings provide further evidence suggesting that PAF might be involved in the process of the TNF-alfa-induced cytotoxicity of L929 mouse fibroblasts.

L111 ANSWER 36 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92114101 EMBASE
DOCUMENT NUMBER: 1992114101
TITLE: From proteins to protein interacting drugs.
AUTHOR: Richards B.
CORPORATE SOURCE: British Bio-Technology Ltd, Watlington Road, Cowley, Oxford, OX4 5LY, United Kingdom
SOURCE: Journal of Pharmacy and Pharmacology, (1992) 44/SUPPL. 1 (172-177).
ISSN: 0022-3573 CODEN: JPPMAB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L111 ANSWER 37 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 90171115 EMBASE
DOCUMENT NUMBER: 1990171115
TITLE: Inhibition of protein kinase C, (sodium plus potassium)-activated adenosine triphosphatase, and sodium pump by synthetic phospholipid analogues.
AUTHOR: Zheng B.; Oishi K.; Shoji M.; Eibl H.; Berdel W.E.; Hajdu J.; Vogler W.R.; Kuo J.F.
CORPORATE SOURCE: Department of Pharmacology, Emory University School of Medicine, Atlanta, GA 30322, United States
SOURCE: Cancer Research, (1990) 50/10 (3025-3031).
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The effects and modes of action of certain antineoplastic phospholipid analogues (racemic 1-O-octadecyl-2-O-methyl glycero-3-phosphocholine, BM 41.440, JH-1, **CV-3988**, and HePC) on (sodium plus potassium)-activated adenosine triphosphatase (Na,K-ATPase) and sodium pump activities were investigated. Inhibition of Na,K-ATPase in purified rat brain synaptosomal membranes by these lipids, in contrast to ouabain, was subject to membrane surface dilution and unaffected by whether the reaction was started with KCl, NaCl, or ATP. Kinetic analysis indicated that the analogues, again dissimilar to ouabain, were likely to interact directly or indirectly with sodium-binding sites of Na,K-ATPase located at the intracellular surface of the plasma membrane, a conclusion also supported by studies using the inside-out vesicles of human erythrocyte membranes. The studies also showed that ouabain (but not the lipids) increased the affinity constant of Na,K-ATPase for K+, whereas the lipids (but not ouabain) increased that for Na+. The lipids also inhibited 86Rb uptake by intact human leukemia HL60 cells at potencies quite comparable to those seen for inhibition of purified protein kinase C or Na,K-ATPase. It is suggested that Na,K-ATPase (sodium pump) might represent a hitherto unrecognized site of action for the lipid analogues, and that the antineoplastic effects of the agents might be due to, in part, inhibition of both protein kinase C and Na,K-ATPase and perhaps other membrane-associated enzymes.

L111 ANSWER 38 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 89091601 EMBASE
DOCUMENT NUMBER: 1989091601
TITLE: Platelet-activating factor-induced phosphoinositide metabolism in differentiated U-937 cells in culture.
AUTHOR: Barzaghi G.; Sarau H.M.; Mong S.
CORPORATE SOURCE: Laboratory for Cardiovascular Clinical Pharmacology, Instituto di Ricerche Farmacologiche 'Mario Negri', Milano, Italy
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1989) 248/2 (559-566).
ISSN: 0022-3565 CODEN: JPETAB
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Human monocytic leukemic U-937 cells, when differentiated with dimethylsulfoxide to macrophage-like state, express receptors for platelet-activating factor (PAF). In the differentiated U-937 cells, PAF induced hydrolysis of phosphoinositides and synthesis of inositol phosphates. PAF-induced production of inositol phosphates was rapid, concentration-dependent and was inhibited by a receptor antagonist **CV3988**, indicating that it was mediated via a specific receptor. In fura-2-loaded, differentiated U-937 cells, PAF induced immediate and concentration-dependent calcium mobilization ([Ca++](i)) that was inhibited by **CV3988**, but not by calcium channel blockers. Addition of an increasing concentration of calcium chelator, ethylene glycol bis(.beta.-aminoethyl ether)-N,N'-tetraacetic acid, to the medium inhibited a large fraction (.apprx.75%) of PAF receptor-induced [Ca++](i) mobilization thus suggesting the majority of [Ca++](i) mobilization was originated from extracellular milieu and a small portion (.apprx.25%) was originated from intracellular sources. The inositol phosphate production induced by PAF, however, was independent from the extracellular calcium

and was not inhibited by the addition of ethylene glycol bis(.beta.-aminoethyl ether)-N,N'-tetraacetic acid. Neither [Ca++](i) mobilization or phosphoinositide metabolism in U-937 cells was sensitive to treatment of pertussis toxin, but both types of effects were sensitive to treatment by an inhibitor of phospholipase C, manoalide. These results suggest that in differentiated U-937 cells PAF receptor is coupled through a pertussis toxin-insensitive guanine nucleotide binding protein to a phosphoinositide specific phospholipase C. Inositol-trisphosphate, and possibly diacylglycerol, could be the intracellular messengers for PAF receptor in U-937 cells.

L111 ANSWER 39 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 88062715 EMBASE
DOCUMENT NUMBER: 1988062715
TITLE: Lack of correlation between cytotoxicity of agonists and antogonists of platelet activating factor (paf-acether) in neoplastic cells and modulation of <3H>-paf-acether binding to platelets from humans in vitro.
AUTHOR: Berdel W.E.; Korth R.; Reichert A.; Houlihan W.J.; Bicker U.; Nomura H.; Vogler W.R.; Benveniste J.; Rastetter J.
CORPORATE SOURCE: Division of Hematology and Oncology, Department of Medicine, Emory University School of Medicine, Atlanta, GA 30322, United States
SOURCE: Anticancer Research, (1987) 7/6 (1181-1188).
ISSN: 0250-7005 CODEN: ANTRD4
COUNTRY: Greece
DOCUMENT TYPE: Journal
FILE SEGMENT: 016 Cancer
023 Nuclear Medicine
025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The 3 ether-lipids ET-18-OCH3, SRI 63-154 and paf-acether, the TLP BM 41.440, the ester-linked 2-LPC and **CV-3988**, were tested for cytostatic/antiproliferative (<3H>-thymidine uptake) and cytotoxic (trypan blue dye exclusion, HTCA) activity in 11 neoplastic human cell lines (U 698-M, Nall-1, Su-DHL-4, RPMI 8226, K 562-4, Li-A, HTB-47, HTB-38, CCL 218, 85 HG-59, 85 HG-63) and 1 ALL in vitro. 2-LPC and paf-acether showed either no, or only minor, **CV-3988** varying activity. There were no significant differences in the activity of ET-18-OCH3, SRI63-154 and BM 41.440, which showed IC50-and LC50-values of .ltoreq.10 .mu.g/ml after incubation periods .gtoreq.48 hours with or during continuous exposure to the cells. The latter three compounds were then tested for interaction with <3H>-paf-acether binding to intact human platelets: ET-18-OCH3 and SRI63-154 reduced <3H>-paf-acether binding in a time-dependent manner. BM 41.440 did not show this interaction. Thus, since the in vitro cytotoxicity of these lipids did not correlate with their modulation of <3H>-paf-acether binding to human platelets, it was concluded that cytotoxicity of ether-lipids is not mediated by specific paf-acether binding sites similar to those present on human platelets. This finding is important for the future design of antineoplastic lipids.

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